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| <b>(51) International Patent Classification <sup>7</sup> :</b><br><b>C07F 15/00, A61K 31/28</b>   | <b>A1</b>  | <b>(11) International Publication Number:</b> <b>WO 00/63219</b><br><b>(43) International Publication Date:</b> 26 October 2000 (26.10.00) |
| <b>(21) International Application Number:</b> PCT/US00/10881<br><b>(22) International Filing Date:</b> 20 April 2000 (20.04.00)<br><b>(30) Priority Data:</b><br>60/130,530 21 April 1999 (21.04.99) US<br>Not furnished 18 April 2000 (18.04.00) US<br><b>(71) Applicant:</b> UNITECH PHARMACEUTICALS, INC. [US/US];<br>4220A Varsity Drive, Ann Arbor, MI 48108 (US).<br><b>(72) Inventor:</b> SHAW, Jiajiu; 3166 Shamrock Ct., Ann Arbor, MI<br>48105 (US).<br><b>(74) Agent:</b> BECKER, Donna, E.; Brinks Hofer Gilson & Lione,<br>P.O. Box 10087, Chicago, IL 60610 (US). | <b>(81) Designated States:</b> AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>With international search report.<br/>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |  |
| <b>(54) Title:</b> PLATINUM COMPLEXES FOR THE TREATMENT OF CANCER   |  |  |
| <b>(57) Abstract</b><br><br>The synthesis and use of a series of novel platinum complexes for the treatment of cancer and AIDS are disclosed. The platinum complexes include cisplatin analogs, carboplatin analogs, and cisplatin and folic acid compounds.  |  |  |

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## PLATINUM COMPLEXES FOR THE TREATMENT OF CANCER

This application claims priority under 35 U.S.C. § 119(e) to United States Provisional Patent Application Serial No. 60/130,530 filed April 21, 1999 and to United States Patent Application No. XX/XXX,XXX, entitled Carboplatin Analogues for the Treatment of Cancer, filed on April 18, 2000.

### FIELD OF THE INVENTION

This invention relates to the syntheses of a series of platinum complexes and to the use of such complexes for the treatment of cancer and AIDS. More specifically, this invention relates to the syntheses of a series of as cisplatin analogs, carboplatin analogs, and cisplatin and folic compounds and the use of these compounds for the treatment of cancer and AIDS.

### BACKGROUND OF THE INVENTION

Cisplatin (*cis*-diaminedichloroplatinum, *cis*-Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>) was the first anticancer platinum drug. It has been used as a chemotherapeutic agent for many years since the discovery of its anti-tumor activity by B. Rosenberg *et. al.* (*Nature*, 1965, 205: 698; *Nature*, 1972, 222: 385).

Chemical & Engineering News (October 23, 1995) reported that "Cisplatin was first synthesized in the 1800s, but its anticancer activity was not discovered until the 1960s. In 1979, it was approved by the Food and Drug Administration for clinical treatment of testicular and ovarian tumors and cancers of the head and neck. Cisplatin and an analog, carboplatin, are now among the most widely used anticancer drugs."

The Physician's Desk Reference (PDR) reports that cisplatin (the commercial name is Platinol®) can be used to treat testicular cancer, ovarian cancer, and bladder cancer. Rosenberg et al., U.S. Patent No. 4,177,263, describes

methods of treating cancer using cisplatin and cisplatin analogs. The compound was shown to be effective for treating leukemia and tumors induced in mice.

After so many years, cisplatin is still being widely used because of its efficacy. However, because of its toxicity and limited use in only certain cancers, numerous modifications have been made in order to come up with better platinum drugs.

One of the cisplatin analogs, carboplatin (Paraplatin®), has been successfully developed and widely prescribed in recent years. As a cisplatin analog, carboplatin has become a more popular platinum drug because it has a better therapeutic index. In other words, carboplatin has a better efficacy/toxicity ratio when used in the treatment of cancer. Nevertheless, carboplatin still has significant side effects. Therefore, there is a need to further improve carboplatin to reduce its toxicity.

Many people have attempted to change the ligand on platinum to make cisplatin analogs in order to reduce the toxicity or improve the efficacy. Examples are disclosed in K. C. Tsou, *et al.* (*J. Clin. Hemat. Oncol.*, 7: 322 (1977)); R. J. Speeder *et al.* (*J. Clin. Hemat. Oncol.*, 7: 210 (1977)); A. Mathew *et al.* (*Chem. Comm.*, 222 (1979)); D. Rose, *et al.* (*Cancer Treatment Reviews*, 12: 1 (1985)); and D. Alberts *et al.* (*Cancer Treatment Reviews*, 12, 83 (1985)).

Several dinuclear platinum(II) complexes have been synthesized in recent years. Examples include complexes made by N. Farrell and co-workers as disclosed in U.S. Patent Nos. 5,107,007 and 5,770,591. Other examples include dinuclear platinum(II) complexes as disclosed by Shaw in U.S. Patent Application Serial No. 09/178,055.

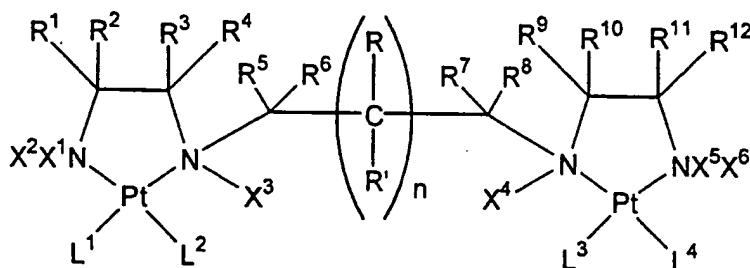
Many articles have been published which suggest modifying the composition of the dosage forms of cisplatin by combining it with other compounds. For example, cisplatin has been used in combination with caffeine as disclosed in H. Yasutake *et al.* (*Gan to Kagaku Ryoho*, 16: 2031-2038, (1989)); and in H. Tsuchiya (*Kanazawa Daigaku Juzen Igakkai Zasshi*, 97: 543-556 (1988)). Cisplatin has also been used in combination with cytosine arabinoside

and the combination has shown some advantages as shown by J. Berek *et al.* (*Obstet. Gynecol.*, 74, 663-666 (1989)). Another combination, cisplatin and novobiocin, has also been shown to be advantageous by P. Eder *et al.* (*Cancer Research*, 49: 595-598 (1989) and U.S. Patent No. 5,130,145).

## BRIEF SUMMARY

This invention discloses the syntheses of new platinum complexes and the use of these complexes to treat cancer and AIDS.

In one aspect, the present invention comprises compounds of formula (I):



wherein  $n$  is 0, 1, 2, 3, 4, 5, or 6;

each of  $L^1$ ,  $L^2$ ,  $L^3$ , and  $L^4$ , independently, is Cl or Br;

each of  $R$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$ ,

independently, is hydrogen, lower alkyl, lower alkoxy, alkyl carboxylate or alkyl carboxylic acid salt; or each of  $CR^1R^2$  (that is,  $R^1$  and  $R^2$  together with the carbon which they substitute),  $CR^3R^4$ ,  $CR^5R^6$ ,  $CR^7R^8$ ,  $CR^9R^{10}$ ,  $CR^{11}R^{12}$ , and  $CRR^1$  independently, is  $C=O$ , and

each of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$ , and  $X^6$ , independently, is hydrogen, lower alkyl, alkyl carboxylate or alkyl carboxylic acid salt.

The dinuclear platinum complexes of the present embodiment can have 1 to 4 Pt-Cl bonds, which are labile and responsible for binding to DNA. The overall charge for the complex can be 0, +1, and +2.

In another aspect, this invention includes novel pharmaceutical compositions comprising cisplatin and folic acid. Optionally, pharmaceutical excipients can be present in these compositions.

Predominantly, cisplatin binds onto deoxyguanosine of DNA. However, cisplatin also binds to other deoxynucleosides or nucleosides. Cisplatin causes many side effects due to its non-selectivity. Therefore, reducing the toxicity of cisplatin is a very important issue. In this embodiment of the present invention, the novel composition comprising cisplatin and folic acid has demonstrated the surprising result of decreased toxicity at lower calcium concentrations. These results indicate that the novel composition has a broader dosage range than cisplatin at physiologic calcium concentration.

In addition to being used to treat cancer, since cisplatin binds to DNA or RNA, this composition can also be used to treat viruses, such as Human Immunodeficiency Virus (HIV), to bind its DNA or RNA and kill the virus. Thus, the composition may be used for the treatment of Acquired Immune Deficiency Syndrome (AIDS). The composition may also be used in combination with other well known AIDS drugs, such as 3'-azidothymidine (AZT), to interfere with the HIV enzyme reverse transcriptase and to achieve the goal of hampering the reproduction of HIV.

In yet another aspect, the present invention comprises the syntheses of a series of platinum(II) complexes as carboplatin analogs for the treatment of cancer. These platinum(II) complexes can be reversibly activated/deactivated in media with different pH values. These platinum(II) complexes can have significantly reduced drug resistance relative to cisplatin or carboplatin because the ligands are abundant biologically. In addition, they can be used in treating cancers that are not treated by cisplatin or carboplatin because of the variety of the ligands.

Other objects, features, and advantages of the present invention will become apparent from the following detailed description. It should be understood that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effects of Carboplatin on the human hepatoma cell line, Hep 3B.

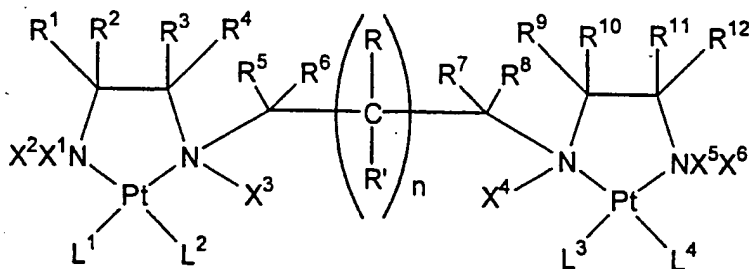
Figure 2 shows the effects of Compound 030399 on the human hepatoma cell line, Hep 3B.

Figure 3 shows the effects of Carboplatin and Compound 030399 on the human colon carcinoma cell line, Caco-2.

## DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

In one embodiment, this invention comprises the syntheses of a group of new cisplatin analogs, dinuclear platinum complexes, and the use of these cisplatin analogs to treat cancer.

The complexes of the present embodiment have the formula (I):



wherein n is 0, 1, 2, 3, 4, 5, or 6;  
 each of  $L^1$ ,  $L^2$ ,  $L^3$ , and  $L^4$ , independently, is Cl or Br;  
 each of  $R$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$ ,  
 independently, is hydrogen, lower alkyl, lower alkoxy, alkyl carboxylate or alkyl  
 carboxylic acid salt; or each of  $CR^1R^2$  (that is,  $R^1$  and  $R^2$  together with the carbon  
 which they substitute),  $CR^3R^4$ ,  $CR^5R^6$ ,  $CR^7R^8$ ,  $CR^9R^{10}$ ,  $CR^{11}R^{12}$ , and  $CRR'$   
 independently, is C=O, and  
 each of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$ , and  $X^6$ , independently, is hydrogen, lower alkyl,  
 alkyl carboxylate or alkyl carboxylic acid salt, or a pharmaceutically acceptable  
 salt thereof.

As used herein, "lower alkyl" means a linear, branched, or cyclic  
 hydrocarbon group containing from about 1 to 6 carbons, preferably from 1 to 3  
 carbons. Preferred lower alkyl groups include methyl, ethyl, and propyl.

"Lower alkoxy" means a linear or branched chain alkoxy group from about  
 1 to 6 carbons, preferably from 1 to 3 carbons. Preferred lower alkoxy groups  
 include methoxy, ethoxy, and propoxy.

"Alkyl carboxylate" means a linear or branched hydrocarbon group  
 containing from about 1 to 6 carbons, preferably from 1 to 3 carbons, and a  
 carboxylate group ( $-COOH$ ).

Salts of alkyl carboxylates include inorganic or organic salts such as  
 $[-CH_2COO][Na]^+$ ,  $[-(CH_2)_2COO][N(CH_3)_4]^+$ , etc.

The dinuclear platinum complexes of the present embodiment can have 1 to  
 4 Pt-Cl bonds, which are labile and responsible for binding to DNA. The overall  
 charge for the complex can be 0, +1, or +2.

The dinuclear complex comprises  $[PtCl_4]^{+2}$  and triethylenetetraamine or its  
 derivatives, at a stoichiometric ratio of about 1.8:1 to about 2:0.8, preferably 1.9:1  
 to 2:0.9, and most preferably at the ratio of about 2:1.

The chelating agents may include triethylenetetraamine and its derivatives.  
 Suitable derivatives include  $N,N'$ -bis(2-dimethylaminoethyl)oxamide,  $N,N'$ -bis(2-  
 aminoethyl)oxamide, and  $N,N'$ -bis(2-aminoethyl)ethylenediamine.



The labile Pt-Cl bonds on the new complex chelate with DNA in the same fashion that cisplatin does. Therefore, the complex may be used to treat cancer. The complex can be more powerful than cisplatin because it has two levels of chelating effects on DNA. Besides the cisplatin effects, an additional level of chelating effect exists because of the carbon chain that connects the two Pt centers.

This class of cisplatin analogs maintains the original active sites of cisplatin (i.e., two Pt-Cl bonds in *cis* position). In addition, there is a bridge (the carbon chain) connecting the two Pt centers creating another level of chelating effect.

Specific examples of the syntheses of these complexes are shown in the examples below. The current theory of the mode of action of these complexes is described below, but their action is not limited to these mechanisms. Because there are two Pt centers in each complex, several scenarios may be explained as follows (Cl may be replaced by Br in all three scenarios): (1) One Pt-Cl bond on each Pt: In this case, each of the two Pt-Cl bonds (one on each Pt) serves as an active site of a bidentate chelating agent. (2) Two Pt-Cl bonds on each Pt: In this case, each Pt has two Pt-Cl bonds in the *cis* position, which functions as cisplatin. In addition, because the two pairs of *cis*-[Pt-Cl] bonds are connected by the carbon chain, each *cis*-[Pt-Cl] pair can act as an active site of a larger bidentate ligand and attack DNA in the way similar to that in scenario 1. (3) Two Pt-Cl bonds on one Pt and one Pt-Cl bond on another Pt: In this case, one pair of *cis*-[Pt-Cl] bonds may act just like cisplatin does. The other Pt-Cl bond would act in coordination with the pair of *cis*-[Pt-Cl] bonds to form two active sites of a larger bidentate ligand.

The complex of the present invention may be used to treat cancers including, but not limited to, testicular cancer, ovarian cancer, bladder cancer, breast cancer, and skin cancer. ♥

The complex may be administered to a cancer patient orally, or by subcutaneous or intravenous injection, or by means of an implanted reservoir, or by means of applying on the cancerous skin.

The injectable dosages are normally in the form of an aqueous solution. If necessary, pharmaceutically-acceptable suspension or emulsion may be employed. Typically, such a composition contains the complex at a concentration of 0.005% - 0.25% (0.05 mg/mL - 2.5 mg/mL), more commonly 0.01% - 0.1% (0.1 mg/mL - 1 mg/mL). The dosage administered by injection comprises the complex in the range of 5 - 1,000 mg in the first day of every 1 - 4 weeks depending upon the patient. Typically, one might administer a dosage of 50 - 400 mg in the first day of every 1 - 4 weeks to a patient having a body weight of 40 - 100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range.

The complex may also be administered orally, for example, as a solution, a suspension, an emulsion, or as tablets or capsules. Solution and suspension for oral administration are typically of about the same concentration as those used for injection. However, when administering the complex orally, it may be desirable to use a higher dosage rate than when administering it by injection. For example, a dosages containing 10 - 1,500 mg of the complex in the first day of every 1 - 4 weeks may be used. Typically, one might administer a dosage containing 50 - 600 mg of the complex in the first day of every 1 - 4 weeks. In preparing such tablets or capsules, standard tablet or capsule making techniques may be employed. If desired, suitable pharmaceutically acceptable excipients such as starch, mannitol, cellulose, talc, surfactant, or lactose may be used in preparing the tablets or capsules. Capsules may also be prepared using soft gelatin as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules which release the active ingredient over a period of several hours.

It may also be used in combination or in tandem with other known anticancer drugs, including but not limited to Taxol® (paclitaxel) and doxorubicin.

The complexes of the present embodiment can also be used in the treatment of AIDS (Acquired Immune Deficiency Syndrome). Because of the ability of these complexes to hamper the DNA or RNA replication process, these complexes

can be effective against the HIV (Human Immunodeficiency Virus) and may be used for the treatment of AIDS. These complexes can also be used in combination or in tandem with other known AIDS drugs, including, but not limited to, AZT (3'-azidothymidine), to interfere with the HIV enzyme reverse transcriptase and achieve better therapeutic results.

These complexes can be administered to an AIDS patient in the same way as in the treatment of a cancer patient. A dosage containing 10 - 600 mg of the complex in the first day of every 1 - 4 weeks can be administered. When used in conjunction with a well known drug for AIDS, such as AZT, the dosage can be suitably reduced. A dosage containing 5 - 1,500 mg of the complex in the first day of every 1 - 4 weeks can be administered; the dosage and the method of administration of the drug for AIDS is the same as it is normally used for cancer treatment.

#### Example 1

2:1 Complex of tetrachloroplatinum (II) and triethylenetetraamine.

A 0.01 molar aqueous solution of triethylenetetraamine (e.g., 0.073 g in 50 mL) was slowly added into a 0.02 M aqueous solution of potassium tetrachloroplatinum (II), light red in color, (e.g., 0.415 g in 50 mL) while mixing. The mixed solution was light brown in color. The reaction flask was hand shaken for a few minutes and kept at room temperature for about one week. During this time, the flask was loosely capped. The burgundy colored crystalline particles were precipitated out on the bottom. A small portion of the crystals, with smaller particle size, were floating on the top. The mixture was filtered and washed with ice water to obtain the clean crystalline burgundy particles.

C,H,N analysis results: C (11.1%), H(2.41%), N(7.97%).

Melting point: 277 - 278 °C (decomposed).

### Example 2

2:1 complex of tetrachloroplatinum (II) and N,N'-bis(2-dimethylaminoethyl) oxamide,  $(\text{CH}_3)_2\text{N}(\text{CH}_2)_2\text{N}(\text{C}=\text{O})_2\text{N}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ .

A 0.01 Molar aqueous solution of N,N'-bis(2-dimethylaminoethyl)oxamide (e.g., 0.1424 g in 50 mL) was slowly added to a 0.02 M aqueous solution of potassium tetrachloroplatinum (II), light red in color, (e.g., 0.415 g in 50 mL) while mixing. The mixed solution was light brown in color. The reaction flask was hand shaken for a few minutes and kept at room temperature for about one week. During this time, the flask was loosely capped. The orange colored crystalline particles were precipitated out on the bottom and the side of the container. The mixture was filtered and washed with ice water to obtain the pure crystalline orange crystals.

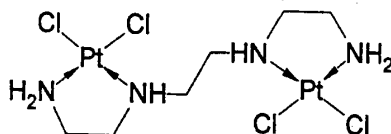
C,H,N analysis results: C (15.72%), H(3.06%), N(7.06%).

Melting point: 213 – 214 °C (decomposed).

### Example 3

The *in-vitro* effects of Compound 030399 on the human hepatoma cell line, Hep 3B.

The compound used in this experiment is designated Compound 030399 and has the following chemical formula. It is a member of the class of compounds of Formula (I) above.



The human hepatoma cell line, Hep 3B, was used. The cells were grown in MEM media containing 10% heat-inactivated fetal bovine serum, 100 units/ml penicillin, 100 µg/ml streptomycin, and 2.5 µg/ml fungizone at 37°C in a 5% carbon dioxide incubator. Cells were initially grown in 75 cm<sup>2</sup> (T75) flasks.

A 6-well plate with about 60% confluent cells in each well was used for each experiment. The 6-well plate was prepared as follows: In a confluent T75 flask, cells were trypsinized with 3 ml of trypsin solution. After incubation with trypsin at 37°C for 5 minutes, 7 ml of fresh media was added and 0.5 ml of the resulting cell suspension was transferred into each well of the 6-well plate containing 2 ml of fresh media. Cells were treated on the day following the preparation of the 6-well plate.

Stock solutions were all sterile-filtered. For the carboplatin-treated cells, 100X carboplatin stocks were made in water and 20  $\mu$ l of the corresponding stock solution was added to each well with 2 ml of fresh media. For the Compound 030399-treated cells, 50  $\mu$ M of 030399 in media was made and serially diluted with media to achieve the final concentration in each well.

Two days after treatment at 37°C, cells were harvested and quantified using a Coulter Counter. To harvest, the cells were trypsinized with 0.5 ml of trypsin solution for 5 minutes at 37°C. Then 0.5 ml of fresh media was added to each well. Cell suspensions were transferred to a culture tube containing 1 ml of Isoton II. Upon vigorous mixing, a 1 ml aliquot was transferred to a new culture tube to make a duplicate sample (2 samples per well of 1 ml each). Cells were quantified by adding 0.6 ml of vigorously mixed cell suspension to 10 ml of Isoton II in a counting container. The Coulter Counter was set to count cells with a diameter between 10 - 20  $\mu$ m.

Each set of experiments was performed two times, i.e. two 6-well plates for each compound tested. All cell culture plasticware was purchased from Fisher. Media and antibiotics were purchased from Gibco.

In each experiment, the cells were treated with carboplatin and Compound 030399. Carboplatin is a well known anti-neoplastic agent, and serves as a positive control in these experiments. There is also a negative control in each experiment in which cells were grown in the absence of drug. Each of the experiments was performed in duplicate.

The results for the treatment of the Hep 3B cells with carboplatin or Compound 030399 is summarized in Table 1, below.

Table 1

| Hep 3B Cells                    |                     |  |                     |
|---------------------------------|---------------------|--|---------------------|
| Carboplatin<br>Conc. ( $\mu$ M) | % Cell<br>Viability | Compound<br>030399<br>Conc. ( $\mu$ M) | % Cell<br>Viability |
| 0 $\mu$ M (control)             | 100                 | 0 $\mu$ M (control)                    | 100                 |
| 2.5 $\mu$ M                     | 45.3 $\pm$ 0.9      | 2.5 $\mu$ M                            | 92.4 $\pm$ 14.6     |
| 5 $\mu$ M                       | 33.4 $\pm$ 7.9      | 5 $\mu$ M                              | 73.7 $\pm$ 8.4      |
| 10 $\mu$ M                      | 25.6 $\pm$ 0.9      | 10 $\mu$ M                             | 64.5 $\pm$ 8.       |
| 25 $\mu$ M                      | 24.1 $\pm$ 3.7      | 25 $\mu$ M                             | 39.0 $\pm$ 3.9      |
| 50 $\mu$ M                      | 25.0 $\pm$ 0.7      | 50 $\mu$ M                             | 29.3 $\pm$ 2.3      |

In this experiment, using the human hepatoma cell line, Hep 3B, the  $IC_{50}$  for carboplatin and Compound 030399 were 5 and 18  $\mu$ M, respectively. These results for carboplatin and Compound 030399 are shown in Figure 1 and Figure 2, respectively. The  $IC_{50}$  values for the two compounds are comparable, and both carboplatin and Compound 030399 significantly inhibited the growth of the human hepatoma cell line, Hep 3B.

#### Example 4

The *in-vitro* effects of Compound 030399 on the human colon carcinoma cell line, Caco-2.

In this experiment, the human colon carcinoma cell line, Caco-2, was used. The experiment of Example 4 was carried out under the same conditions as described in Example 3, above, except for the use of the human colon carcinoma cell line, Caco-2, instead of the human hepatoma cell line, Hep 3B.

The treatment of the Caco-2 cells with carboplatin or Compound 030399 is summarized in Table 2.

Table 2

| Caco-2 Cells                    |                     |  |                     |
|---------------------------------|---------------------|--|---------------------|
| Carboplatin<br>Conc. ( $\mu$ M) | % Cell<br>Viability | Compound<br>030399<br>Conc. ( $\mu$ M) | % Cell<br>Viability |
| 0 $\mu$ M (control)             | 100                 | 0 $\mu$ M (control)                    | 100                 |
| 2.5 $\mu$ M                     | 88.9 $\pm$ 1.9      | 2.5 $\mu$ M                            | 95.1 $\pm$ 2.1      |
| 5 $\mu$ M                       | 80.9 $\pm$ 0.3      | 5 $\mu$ M                              | 94.8 $\pm$ 1.3      |
| 10 $\mu$ M                      | 59.4 $\pm$ 6.8      | 10 $\mu$ M                             | 72.7 $\pm$ 1.3      |
| 25 $\mu$ M                      | 45.8 $\pm$ 3.9      | 25 $\mu$ M                             | 61.0 $\pm$ 2.7      |
| 50 $\mu$ M                      | 38.4 $\pm$ 1.2      | 50 $\mu$ M                             | 15.5 $\pm$ 4.3      |

In this experiment, using the human colon carcinoma cell line, Caco-2, the  $IC_{50}$  for carboplatin and Compound 030399 were 3.8 and 6.2  $\mu$ M, respectively. These results are shown in Figure 3. The  $IC_{50}$  values for the two compounds are comparable, and both carboplatin and Compound 030399 significantly inhibited the growth of the human colon carcinoma cell line, Caco-2.

In another embodiment, the present invention comprises a novel pharmaceutical composition comprising cisplatin and folic acid. The pharmaceutical composition has a mole ratio of cisplatin to folic acid in the range of about 1:0.05 to 1:1, preferably 1:0.1 to 1:0.8, and most preferably 1:0.2 to 1:0.5.

Cisplatin is commercially available from many sources such as Sigma Chemical Company and Alfa Aesar. Folic acid is also commercially available from a variety of sources such as Spectrum Quality Products, Inc. and Sigma Chemical Company.

The composition of the present embodiment may optionally include other pharmaceutically acceptable excipients. Suitable pharmaceutical excipients are customary and physiologically acceptable such as sodium bicarbonate, mannitol, lactose, sodium chloride, phosphates, water, ethanol, hydrochloric acid, magnesium stearate, cellulose, starch, polyethylene glycol, etc. Therefore, the

composition may be in a liquid or solid dosage form suitable for parenteral or oral administration to a patient.

One method of preparing the composition of the present embodiment is as follows: 1. Combine cisplatin and folic acid in a solvent at a molar ratio of about 1:0.05 to 1:1 so that the percentage of cisplatin is 0.005% to 0.25% in the aliquot. The solvent can be water containing a suitable amount of sodium bicarbonate, 0.1% to 99% methanol in water, 0.1% to 99% ethanol in water, 0.1% to 99% acetone in water, 0.05 % to 5.0 % sodium chloride in water, 0.0001 N to 1.0 N hydrochloric acid, or a mixture of such solvents. 2. Stir the aliquot until it becomes a solution. 3. Filter through a filter, preferably a filter with a porosity of between 0.1  $\mu\text{m}$  to 1.0  $\mu\text{m}$ , more preferably between 0.2  $\mu\text{m}$  to 0.45  $\mu\text{m}$ , and collect the filtrate. 4. Optionally, the filtrate from step (3) can be dried under vacuum or by other standard pharmaceutical techniques. 5. Optionally, the dried composition from step (4) can be reconstituted into a solution or a suspension by a suitable solvent. Typically, the percentage of cisplatin is 0.005% to 0.25%, preferably 0.01 % to 0.1 %. Suitable solvents include water containing sodium bicarbonate, ethanol, 0.1% to 90% ethanol in water, 0.05 % to 5.0 % sodium chloride in water, 0.0001 N to 1.0 N hydrochloric acid, or a mixture of such solvents. 6. Optionally, the dried composition from step (4) can be blended with one or more physiologically acceptable pharmaceutical excipient(s). The resulting product can be encapsulated or compressed into capsules or tablets using standard pharmaceutical techniques.

This composition can be used to treat any cancers that can be treated by cisplatin, as well as other forms of cancer. These include testicular cancer, ovarian cancer, bladder cancer, leukemia, and cancers of the head and neck. This composition can also be used to treat breast cancer as indicated by the *in-vitro* studies in Example 8.

The composition may be administered to a cancer patient orally, or by subcutaneous or intravenous injection, or by means of an implanted reservoir, or by means of applying on the cancerous skin.



The injectable compositions are normally in the form of an aqueous solution. If necessary, a pharmaceutically acceptable suspension may be employed. Typically, such a solution contains cisplatin at a concentration of about 0.005% - 0.25% (0.05 mg/mL - 2.5 mg/mL), and more commonly about 0.01% - 0.1% (0.1 mg/mL - 1 mg/mL). The dosage administered by injection comprises cisplatin in the range of about 5 - 1,000 mg in the first day of every 1 - 4 weeks depending upon the patient. Typically, one might administer a dosage of about 50 - 400 mg in the first day of every 1 - 4 weeks to a patient having a body weight of about 40 - 100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range.

The composition may also be administered orally, for example, as a solution or a suspension or as tablets or capsules. Solution and suspension for oral administration are typically of about the same concentration as those used for injection. However, when administering the drug orally, it may be desirable to use a higher dosage rate than when administering it by injection. For example, a dosage containing about 10 - 1,500 mg cisplatin in the first day of every 1 - 4 weeks can be used. Typically, one might administer a dosage containing about 50 - 600 mg cisplatin in the first day of every 1 - 4 weeks. In preparing such tablets or capsules, standard tablet or capsule making techniques are employed. If desired, suitable pharmaceutically acceptable excipients such as starch, mannitol, cellulose or lactose may be used in preparing the tablets or capsules. Capsules may also be prepared using soft gelatin as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules which release the active ingredient over a period of several hours.

This composition can also be used in the treatment of AIDS because of the ability of cisplatin to hamper the DNA or RNA replication process. This composition can be administered to an AIDS patient in the same way as in the treatment of a cancer patient. A composition having about 10 - 600 mg of cisplatin in the first day of every 1 - 4 weeks can be administered.

The composition can also be used in combination with other well known AIDS drugs, including, but not limited to AZT, to interfere with the HIV enzyme reverse transcriptase and achieve better therapeutic results. When used in conjunction with a well known drug for AIDS, such as AZT, the dosage of cisplatin in the composition may be suitably reduced. A composition having 5 - 1,500 mg of cisplatin in the first day of every 1 - 4 weeks may be administered. The dosage and the method of administration of the composition for the treatment of AIDS is the same as it is normally used for cancer treatment.

Several examples of the cisplatin and folic acid composition are shown in the following examples.

#### Example 5

Method of Preparation of Cisplatin and Folic Acid Composition.

1. Weigh 30 mg of cisplatin (about 0.2 mmole).
2. Weigh 250 mg of folic acid (containing 8.5 % water) (about 0.1 mmol).
3. Weigh 500 mg of sodium bicarbonate.
4. Add the weighed cisplatin, folic acid, and sodium bicarbonate to 500 mL of water.
5. Stir the aliquot for 30 minutes or until it becomes a solution.
6. Filter the solution through a suitable filter with a porosity of 0.2  $\mu$ M and collect the filtrate. The final liquid composition has a cisplatin concentration of about 06 % and the mole ratio of cisplatin to folic acid is about 1:0.5.

#### Example 6

Alternate Method of Preparation of Cisplatin and Folic Acid Composition.

1. Weigh 30 mg of cisplatin (about 0.2 mmole) and add it to 200 mL of water.
2. Weigh 250 mg of folic acid (about 0.1 mmole) and add it to 300 mL of water containing 600 g of sodium bicarbonate.
3. Mix the two aliquots from step 1 and from step 2 in a suitable container.
4. Stir the aliquot (from step 3) overnight.
5. Filter the solution through a suitable filter with a porosity of 0.2  $\mu$ M and collect the filtrate.
6. Dry the filtrate by a rotary evaporator or other standard

pharmaceutical technique. The final solid composition has a mole ratio of cisplatin to folic acid of about 1:0.5.

#### Example 7

Method of Encapsulation of Cisplatin and Folic Acid Composition.

1. Weigh 100 g of the dry composition made according to the procedures in Example 6; add it to 300 g of lactose; mix till the blend is uniform. 2. Add the blend made from step 1 to 400 g of mannitol and mix well. 3. Add 10 g of magnesium stearate into the blend made from step 2 and mix for three minutes. 4. Encapsulate the blend from step 3 into suitable capsules so that each capsule contains approximately 100 mg of cisplatin. The final composition in each capsule contains 100 mg cisplatin and the mole ratio of cisplatin to folic acid is about 1:0.5.

#### Example 8

The *in-vitro* effects of Compound #801C on the human breast cancer cell line MCF-7.

The composition prepared according to Example 5 (identified as #801C) and cisplatin were evaluated, side by side, for their biologic activities against the human breast cancer cell line, MCF-7, and against the normal human mammary cell line, NHMC. The results are shown in Tables 3-5.

Table 3

Percent Inhibition in MCF-7 Cells

|           | 25 $\mu$ L | 10 $\mu$ L | 5 $\mu$ L |
|-----------|------------|------------|-----------|
| Cisplatin | 92%        | 49%        | 25%       |
| #801C     | 83%        | 44%        | 34%       |

The inhibition of MCF-7 cell growth are substantially similar for cisplatin and #801C.

Table 4

Percent Inhibition in NHMC Cells Grown in RPMI-10

|           | 1/100 | 1/200 | 1/400 |
|-----------|-------|-------|-------|
| Cisplatin | 88%   | 46%   | 0%    |
| #801C     | 67%   | 31%   | 20%   |

The inhibition of growth of NHMC cells is not significantly different for cisplatin and #801C.

Table 5Percent Inhibition in NHMC Cells Grown at  
Low Calcium Concentration (40  $\mu$ M)

|           | 1/100 | 1/200 | 1/400 |
|-----------|-------|-------|-------|
| Cisplatin | 32%   | 31%   | 27%   |
| #801C     | 24%   | 13%   | 1%    |

The inhibition of NHMC cell growth by #801C is significantly lower than that of cisplatin indicating that #801C may be less toxic than cisplatin under physiologic conditions at lower calcium concentrations.

Another embodiment of the present invention relates to a series of platinum(II) complexes for use as carboplatin analogs. These platinum(II) complexes are similar to carboplatin in that each complex has two active sites individually protected by carboxylate groups. However, because each carboxylate group is part of the respective bidentate ligand, hydrolysis of the carboxylate only separates it from the Pt(II) ion, but not the molecule. Therefore, both carboxylate groups are able to reattach to Pt(II) under a higher pH condition, such as the normal biological condition. This behavior makes the complexes significantly different from carboplatin, in which carboxylate groups, when hydrolyzed, are permanently separated from the Pt(II) ion. As a result, these platinum(II) complexes can be much less toxic than other platinum drugs.

The carboplatin analogs of the present embodiment can reduce drug resistance after repeated treatment relative to that which is often seen with

cisplatin or carboplatin treatment. Unlike carboplatin, the platinum(II) complexes of this invention utilize the carboxylate of phosphatidylserine,  $\alpha$ -amino acids,  $\beta$ -amino acids, or their derivatives as the ligands. Because the platinum(II) is camouflaged by these ligands, which are abundant in living organisms, these complexes are much less likely to incur drug resistance on repeated treatment.

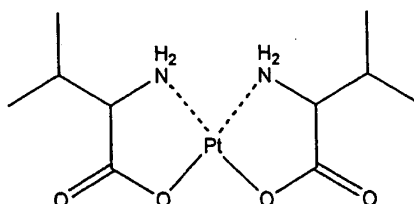
These carboplatin analogs can also expand the number and the types of cancer in which the complexes can be effectively used. Cisplatin and carboplatin have been used only in some cancers, such as testicular and ovarian tumors, cancers of the head and neck, etc. It would be greatly beneficial to expand the use of platinum drugs to treat cancers that are not being treated by cisplatin and carboplatin.

The platinum(II) complexes of the present embodiment can have significantly different physical properties (such as solubility, affinity, permeability, stereo effect, etc.) from those of cisplatin or carboplatin because of the variety of ligands that can be used and because of the ability of amino acids to induce and stabilize some limited conformation themselves or when incorporated into small peptides. Therefore, these complexes can be useful in treating cancers that are not treated by cisplatin or carboplatin.

Therefore, the platinum(II) complexes of this invention have several distinct advantages over carboplatin including (1) they can be reversibly activated and deactivated, (2) they can have a significantly reduced drug resistance, and (3) they can be used to treat cancers that are not treated by cisplatin or carboplatin.

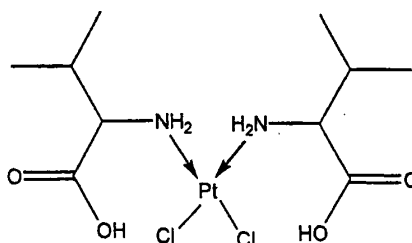
The complexes of the present embodiment can be represented by  $\text{cis-Pt(II)L}^1\text{L}^2$ , wherein each of  $\text{L}^1$  and  $\text{L}^2$ , independently, is the carboxylate of phosphatidylserine, an  $\alpha$ -amino acid, a  $\beta$ -amino acid, or a derivative thereof, wherein each ligand is bidentate with  $-\text{NH}_2$  and  $-\text{COO}^-$  as the binding sites.

The following structure represents *cis*-Pt(valine)<sub>2</sub>:



STRUCTURE 2

Suitable acid, such as HCl, HBr, or HNO<sub>3</sub>, can be added to the complexes to make the free acid form, *cis*-Pt(II)Cl<sub>2</sub>L<sup>1</sup>L<sup>2</sup>, *cis*-Pt(II)Br<sub>2</sub>L<sup>1</sup>L<sup>2</sup> or *cis*-Pt(II)(NO<sub>3</sub>)<sub>2</sub>L<sup>1</sup>L<sup>2</sup> wherein each ligand is monodentate with -NH<sub>2</sub> as the binding site. The structure of PtCl<sub>2</sub>(Valine)<sub>2</sub> is shown as an example:



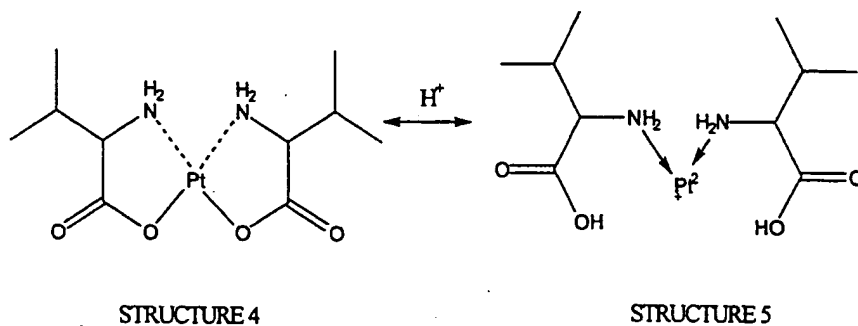
STRUCTURE 3

The  $\alpha$ - amino acid,  $\beta$ -amino acid, or derivative thereof, includes, but is not limited to, alanine, aspartic acid, glutamic acid, glycine, isoleucine, leucine, phenylalanine, proline, serine, threonine, tyrosine, and valine.

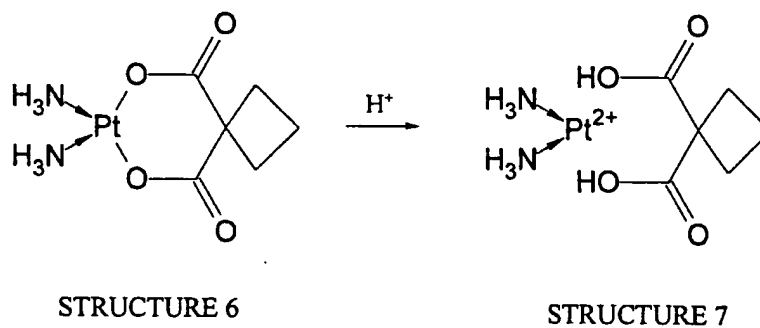
Similar to carboplatin, the platinum(II) complexes of the present embodiment are more likely to be hydrolyzed in a cancerous area where the pH is lower than the normal biological pH. Thus, the two platinum(II) active sites are exposed to interact with DNA. In contrast to carboplatin, the active sites of the

platinum(II) complex in this invention can be re-protected when they enter into a non-cancerous area because of the higher pH value. The activation/deactivation process for the platinum(II) complex is reversible. Therefore, potential side effects can be significantly reduced.

The reversible activation/deactivation reaction of these complexes can be illustrated by the example below:



Whereas for carboplatin, it is a one-way reaction as illustrated below:



Therefore, these platinum(II) complexes or their free acids can be used in treating cancer, and they are expected to have better therapeutic indices than carboplatin and cisplatin.

Another advantage of these platinum(II) complexes is that the platinum(II) ion is camouflaged by amino acids, which are abundant in living organisms. This

fact makes it much less likely to incur drug resistance. Drug resistance for anticancer drugs (such as cisplatin and carboplatin) is well known for repeated treatment.

Yet another advantage of these platinum(II) complexes is that they can be used to treat those cancers that are not treated by cisplatin or carboplatin. This is because of the variety of ligands on these complexes, which covers a wide range of physical/chemical properties, such as solubility, permeability, ionic charge, etc. Therefore, some of these complexes can be used to treat certain types of cancer while others can be best used to treat other types of cancer. In other words, these complexes can be used to treat a much broader range of various types of cancers.

The following examples are included to demonstrate preferred embodiments of the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

#### Example 9

Synthesis of the  $\text{Pt}(\text{L-Tyrosine})_2$  by a heterogeneous method.

Weigh 83 mg (0.2 mmole) of  $\text{K}_2\text{PtCl}_4$  and dissolve it in 100 mL deionized water. Weigh 72 mg (0.4 mmole) of L-tyrosine and add it to the  $\text{K}_2\text{PtCl}_4$  solution. (Note: L-tyrosine is almost insoluble in water.) Adjust the pH to ca. 8 with sodium hydroxide or sodium bicarbonate. Mix the aliquot at about  $35^\circ\text{C}$  for 2-4 days. The aliquot gradually becomes a solution and the color changes from very light tea color to light brown. The UV spectrum shows an additional maximum at about 320 nm. Concentrate the solution under vacuum. Use a suitable solvent system to re-crystallize the product by standard technique.



Example 10

Synthesis of  $\text{Pt}(\text{L-alanine})_2$  by a homogeneous method.

Weigh 83 mg (0.2 mmole) of  $\text{K}_2\text{PtCl}_4$  and dissolve it in 100 mL deionized water. Weigh 35.6 mg (0.4 mmole) of L-alanine and dissolve it in the  $\text{K}_2\text{PtCl}_4$  solution. Adjust the pH to ca. 8 with sodium hydroxide or sodium bicarbonate. Mix the aliquot for 2-4 days at room temperature. The solution gradually changes color from light brown to brown. Concentrate the solution under vacuum. Use a suitable solvent system to re-crystallize the product by standard technique.

Example 11

Synthesis of  $\text{Pt}(\text{L-alanine})(\text{L-tyrosine})$ .

Make  $\text{Pt}(\text{L-alanine})\text{Cl}_2$  according to Example 10 except only half of the L-alanine is required. Add the same number of moles for  $\text{Pt}(\text{L-alanine})\text{Cl}_2$  and L-tyrosine in a suitable amount of water, adjust the pH to ca. 8, and mix it for 2-4 days at room temperature. Proceed as in the previous example to purify the product.

Example 12

Synthesis of  $\text{Pt}(\text{L-alanine})(\text{phosphatidylserine})$ .

The same method as in Example 11 is used to synthesize  $\text{Pt}(\text{L-alanine})(\text{phosphatidylserine})$ .

Example 13

The *in-vitro* effects of sample #011700 on human squamous carcinoma clone cancer cell line (SCC-1).

Sample #011700 is  $\text{PtCl}_2[\text{CH}_3\text{CH}(\text{NH})_2\text{COOH}]_2$  where  $\text{CH}_3\text{CH}(\text{NH})_2\text{COOH}$  is alanine. All cell culture plasticware was purchased from Fisher. Media and antibiotics were purchased from Gibco and Sigma. Cell viability using a Coulter Counter is used to quantify toxicity. SCC-1 cells are grown in MEM media containing 10% Fetal Bovine Serum, 100 units/ml

penicillin, 100 µg/ml streptomycin, and 2.5 µg/ml fungizone at 37°C in a 5% CO<sub>2</sub> incubator. A 6 well dish is inoculated to  $2.0 \times 10^5$  cells/well in a total volume of media of 2 ml. Incubation occurs overnight and the cells are ready for treatment the next day.

Stock solution of sample #011700 is sterile filtered with a 0.22 µm low protein binding syringe filter. Dilutions are made in fresh MEM-10% FBS.

Two days after treatment at 37° C, cells are harvested and quantified using a Coulter Counter. To harvest, all media is removed and 1 ml of 1X trypsin solution is added per well. Trypsin is in the well for approximately 5 minutes at 37°C. After 5 minutes, 1 ml of fresh MEM-10% FBS is added per well. Upon vigorous mixing to ensure breakup of aggregate cells, dilutions are made in Isoton®II ready for cell counts. Each well is counted twice. Thus, duplicate wells plus duplicate counts yield 4 cell counts per parameter above.

The results shown in Table 6 indicate that #011700 shows inhibition of the growth of SCC-1 cells *in-vitro*.

Table 6

| µM #011700 | Cell Count/mL      |
|------------|--------------------|
| 0          | $5.70 \times 10^5$ |
| 20         | $6.00 \times 10^5$ |
| 30         | $5.80 \times 10^5$ |
| 40         | $5.20 \times 10^5$ |
| 50         | $4.40 \times 10^5$ |
| 60         | $3.80 \times 10^5$ |

The platinum(II) complexes of this invention may be formulated with customary pharmaceutical excipients to make suitable dosage forms by standard pharmaceutical techniques and processes. Such excipients include, but are not limited to, starch, cellulose, lactose, magnesium stearate, stearic acid, talc, calcium phosphate, inorganic buffer, organic buffer, surfactant, silicon dioxide, and food color. Two examples of the dosage forms are shown in the examples that follow.

Example 14

An example of making an injectable dosage form.

Weigh 50 mg of Pt(L-Tyrosine)<sub>2</sub> and dissolve it in 1000 mL of deionized water. A suitable amount of phosphate buffer is added to bring the pH to about 7.4. The solution is sterilized to make an injectable dosage form.

Example 15

An example of making an oral dosage form.

A pharmaceutical dosage form for oral administration can be made from the following formulation using standard pharmaceutical techniques and equipment.

100 mg of Pt(L-alanine)(L-tyrosine)

145 mg of lactose

75 mg microcrystalline cellulose

5 mg magnesium stearate

Example 16

An example of administration of a platinum complex of this invention.

A therapeutically effective amount of a platinum(II) complex of this invention is administered to a cancer patient in a suitable dosage form. In a therapeutic regimen, 10 mg – 1000 mg of the platinum(II) complex is administered to a cancer patient by injection once every 1 to 4 weeks. The regimen can be repeated.

Example 17

An alternate example of administration of a platinum complex of this invention.

In a therapeutic regimen, 10 mg – 1000 mg of a platinum(II) complex of the present invention is administered to a cancer patient orally once every 1 to 4 weeks. The regimen can be repeated.

The complexes of the present invention can also be used in the treatment of AIDS (Acquired Immune Deficiency Syndrome). Because these complexes can hamper the DNA or RNA replication process, they can be effective against the HIV (Human Immunodeficiency Virus) and may be used for the treatment of AIDS.

In one aspect, the present invention provides methods for the treatment of various malignancies. Treatment methods involve treating an individual with an effective amount of the platinum(II) complexes of this invention, including cisplatin analogs, cisplatin and folic acid compositions, and carboplatin analogs, as described herein. An effective amount is defined, generally, as that amount sufficient to detectably and repeatedly ameliorate, reduce, minimize, or limit the extent of a disease or its symptoms. More rigorous definitions may apply, including elimination, eradication or cure of disease.

To kill cells, inhibit cell growth, inhibit metastasis, decrease tumor size, and otherwise reverse or reduce the malignant phenotype of tumor cells, using the methods and compositions of the present invention, one would generally contact a "target" cell with the platinum(II) complexes of this invention. This may be combined with compositions comprising other agents effective in the treatment of cancer. These compositions would be provided in a combined amount effective to kill or inhibit proliferation of the cells. This process may involve contacting the cells with platinum(II) complexes of this invention and the agent(s) or factor(s) at the same time. This may be achieved by contacting the cells with a single composition or pharmacological formulation that includes both agents, or by contacting the cells with two distinct compositions or formulations at the same time, wherein one composition includes one or more platinum(II) complex of this invention and the other includes the second agent.

Alternatively, the therapy with the platinum(II) complexes of this invention can precede or follow treatment with the other agent by intervals ranging from minutes to weeks. In embodiments where the other agent and the platinum(II) complexes of this invention are applied separately to the cells, one would generally ensure that a significant period of time did not expire between the time

of each delivery, such that the agent and the platinum(II) complexes of this invention would still be able to exert an advantageously combined effect on the cell. In such instances, one would contact the cells with both modalities within about 12-24 hours of each other and, more preferably, within about 6-12 hours of each other, with a delay time of only about 12 hours being most preferred. In some situations, it may be desirable to extend the time period for treatment significantly, however, where several days (2, 3, 4, 5, 6, or 7 days) to several weeks (1, 2, 3, 4, 5, 6, 7, or 8 weeks) lapse between the respective administrations.

Administration of the therapeutic platinum(II) complexes of the present invention to a patient follow general protocols for the administration of chemotherapeutics, taking into account the toxicity, if any, of the platinum(II) complexes. Treatment cycles can be repeated as necessary. Various standard therapies, as well as surgical intervention, can be applied in combination with the described therapy.

Where clinical application of a particular therapy is contemplated, it is necessary to prepare the complex as a pharmaceutical composition appropriate for the intended application. Generally this entails preparing a pharmaceutical composition that is essentially free of pyrogens, as well as any other impurities that could be harmful to humans or animals. It is also generally desirable to employ appropriate salts and buffers to render the complex stable and allow for complex uptake by target cells.

Aqueous compositions of the present invention comprise an effective amount of the compound, dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium. Such compositions can also be referred to as inocula. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except

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insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

The compositions of the present invention may include classic pharmaceutical preparations. Dispersions also can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Depending on the particular cancer to be treated, administration of therapeutic compositions according to the present invention can be *via* any common route as long as the target tissue is available *via* that route. This includes oral, nasal, buccal, rectal, vaginal or topical. Topical administration would be particularly advantageous for treatment of skin cancers. Alternatively, administration can be by orthotopic, intradermal, subcutaneous, intramuscular, intraperitoneal or intravenous injection. Such compositions can normally be administered as pharmaceutically acceptable compositions that include physiologically acceptable carriers, buffers, or other excipients.

"Pharmaceutically acceptable salt" and "salts thereof" means organic or inorganic salts of the pharmaceutically important molecule. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counterion. The counterion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically important organic molecule may have more than one charged atom in its structure. Situations where multiple charged atoms are part of the molecule may have multiple counterions. Hence, the molecule of a pharmaceutically acceptable salt may contain one or more than one charged atoms and may also contain, one or more than one counterion. The desired charge distribution is determined according to methods of drug administration. Examples of pharmaceutically acceptable salts are well known in the art but, without limiting the scope of the present invention, exemplary presentations can be found in the

Physician's Desk Reference, The Merck Index, The Pharmacopoeia and Goodman & Gilman's The Pharmacological Basis of Therapeutics.

Customary pharmaceutical excipients and standard pharmaceutical techniques can be used to prepare suitable pharmaceutical dosage form of the platinum(II) complexes in this invention. Customary pharmaceutical excipients include, but are not limited to, starch, cellulose, lactose, sucrose, mannitol, magnesium stearate, stearic acid, talc, calcium phosphate, inorganic buffer, organic buffer, surfactant, silicon dioxide, and food color. Pharmaceutical dosage forms include, but are not limited to, tablets, capsules, caplets, solution, suspension, gel, cream, transdermal patch, and implanting reservoir. The dosage form can be an immediate release or a controlled release form. The dosage form can be administered orally or parenterally.

The treatments can include various "unit doses." Unit dose is defined as containing a predetermined quantity of the therapeutic composition calculated to produce the desired responses in association with its administration, *i.e.*, the appropriate route and treatment regimen. The quantity to be administered, and the particular route and formulation, are within the skill of those in the clinical arts. Also of import is the subject to be treated, in particular, the state of the subject and the protection desired. A unit dose need not be administered as a single injection or administration, but may comprise continuous infusion over a set period of time.

Preferably, patients have adequate bone marrow function (defined as a peripheral absolute granulocyte count of  $> 2,000/\text{mm}^3$  and a platelet count of  $100,000/\text{mm}^3$ ), adequate liver function (bilirubin  $< 1.5 \text{ mg/dl}$ ), and adequate renal function (creatinine  $< 1.5 \text{ mg/dl}$ ).

One of the preferred embodiments of the present invention involves the use of the platinum(II) complexes of this invention to treat cancer cells. Target cancer cells include, but are not limited to, cancers of the lung, brain, prostate, kidney, liver, ovary, endometrium, breast, skin, stomach, esophagus, head and neck, testicles, germ cancer, epithelial, colon, small intestine, thyroid, cervix, pancreas, glioblastoma, astrocytoma, oligodendroglioma, ependymomas, neurofibrosarcoma, meningia, lymphatic system, and blood. Of particular interest

are non-small cell lung carcinomas including squamous cell carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas.

According to the present invention, one can treat the cancer by directly injecting a tumor with the therapeutic compositions of the present invention. Alternatively, the tumor can be infused or perfused with the therapeutic composition using any suitable delivery vehicle. Local or regional administration, with respect to the tumor, is also contemplated. Finally, systemic administration can be performed. In certain embodiments, the contacting comprises delivering the therapeutic composition endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, or intratumorally to the subject.

Continuous administration can also be applied where appropriate, for example, where a tumor is excised and the tumor bed is treated to eliminate residual, microscopic disease. Delivery via syringe or catheterization is also contemplated. Such continuous perfusion can take place for a period from about 1-2 hours, about 2-6 hours, about 6-12 hours, about 12-24 hours, about 1-2 days, about 1-2 weeks or longer, following the initiation of treatment. Generally, the dose of the therapeutic composition via continuous perfusion is equivalent to that given by a single or multiple injections, adjusted over a period of time during which the perfusion occurs.

For tumors of  $> 4$  cm, the volume to be administered is about 4-10 mL (preferably about 10 mL), while for tumors of  $< 4$  cm, a volume of about 1-3 mL is used (preferably about 3 mL). Multiple injections delivered as single dose comprise about 0.1 to about 0.5 mL volumes. The tumor may advantageously be contacted by administering the therapeutic composition in multiple injections to the tumor, spaced at approximately 1 cm intervals.

In certain embodiments, the tumor being treated may not, at least initially, be resectable. Treatments with therapeutic composition may increase the resectability of the tumor due to shrinkage at the margins or by elimination of certain particularly invasive portions. Following treatments, resection may be possible. Additional treatments subsequent to resection will serve to eliminate microscopic residual disease at the tumor site. In certain embodiments, tumor



resection may occur prior to the contacting. The tumor resection may be performed one, two, three or more times.

A typical course of treatment, for a primary tumor or a post-excision tumor bed, involves multiple doses. Typical primary tumor treatment involves a 6-dose application over a two-week period. The two-week regimen may be repeated one, two, three, four, five, six or more times. During a course of treatment, the need to complete the planned dosings may be re-evaluated.

Cancer therapies also include a variety of combination therapies with both chemical and radiation based treatments. Combination chemotherapies include, for example, cisplatin, procarbazine, mechlorethamine, cyclophosphamide, camptothecin, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin, etoposide (VP16), tamoxifen, taxol, transplatin, 5-fluorouracil, vincristin, vinblastin, and methotrexate, or any analog or derivative variant thereof.

Other factors that cause DNA damage and have been used extensively include what are commonly known as  $\gamma$ -rays, X-rays, and/or the directed delivery of radioisotopes to tumor cells. Other forms of DNA damaging factors are also contemplated such as microwaves and UV-irradiation. It is most likely that all of these factors effect a broad range of damage on DNA, on the precursors of DNA, on the replication and repair of DNA, and on the assembly and maintenance of chromosomes. Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 weeks), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

In addition, gene therapy is becoming increasingly useful for treating cancers. In such embodiments, expression constructs comprising viral vectors containing the therapeutic genes are used in order to induce an apoptotic effect in cancer cells. The viral vectors may be adenoviral (see for example, U.S. Patent No. 5,824,544; U.S. Patent No. 5,707,618; U.S. Patent No. 5,693,509; U.S. Patent

No. 5,670,488; U.S. Patent No. 5,585,362, each incorporated herein by reference), retroviral (see for example, U.S. Patent No. 5,888,502; U.S. Patent No. 5,830,725; U.S. Patent No. 5,770,414; U.S. Patent No. 5,686,278; U.S. Patent No. 4,861,719, each incorporated herein by reference), an adeno-associated viral (see for example, U.S. Patent No. 5,474,935; U.S. Patent No. 5,139,941; U.S. Patent No. 5,622,856; U.S. Patent No. 5,658,776; U.S. Patent No. 5,773,289; U.S. Patent No. 5,789,390; U.S. Patent No. 5,834,441; U.S. Patent No. 5,863,541; U.S. Patent No. 5,851,521; U.S. Patent No. 5,252,479, each incorporated herein by reference), an adenoviral-adenoviral hybrid (see for example, U.S. Patent No. 5,856,152, incorporated herein by reference) a vaccinia viral or a herpesviral (see for example, U.S. Patent No. 5,879,934; U.S. Patent No. 5,849,571; U.S. Patent No. 5,830,727; U.S. Patent No. 5,661,033; U.S. Patent No. 5,328,688, each incorporated herein by reference) vector. These vectors are contacted with the cancer cells to produce the therapeutic effect. The viral expression construct comprising a nucleic acid encoding a therapeutic anticancer gene can contain any cancer therapy gene known to those of skill in the art including, but not limited to, p53, p16, p21, MMAC1, p73, zac1, C-CAM, BRCA1, Rb, Bax, Bak, Bim, Bik, Bid, Bad gene, Harakiri, Ad E1B, an ICE-CED3 protease, a cytokine such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, TNF, GM-CSF,  $\beta$ -interferon, and  $\gamma$ -interferon. In other embodiments, the therapeutic nucleic acid may be an antisense nucleic acid directed against an oncogene.

It is understood that the expression vectors comprising the therapeutic genes to be used in combination with the compositions of the present invention will further comprise the appropriate promoters, enhancers, and other regulator elements necessary for efficient replication to occur. Such elements are well known to those of skill in the art. Exemplary promoters for use herein include, but are not limited to, CMV IE, SV40 IE, RSV,  $\beta$ -actin, tetracycline regulatable, and ecdysone regulatable. By "treatment," the present invention refers to any event that decreases the growth, kills, or otherwise abrogates the presence of cancer cells

in a subject. Such a treatment can also occur by inhibition of the metastatic potential or inhibition of tumorigenicity of the cells so as to achieve a therapeutic outcome.

Various combinations can be employed. For example, where the platinum(II) complexes of the present invention are represented by "A" and the gene, radiotherapeutic, or chemotherapeutic agent is represented by "B", combinations can include:

|         |         |         |         |         |         |
|---------|---------|---------|---------|---------|---------|
| A/B/A   | B/A/B   | B/B/A   | A/A/B   | A/B/B   | B/A/A   |
| A/B/B/B | B/A/B/B | B/B/B/A | B/B/A/B | A/A/B/B | A/B/A/B |
| A/B/B/A | B/B/A/A | B/A/B/A | B/A/A/B | A/A/A/B | B/A/A/A |
| A/B/A/A | A/A/B/A |         |         |         |         |

The terms "contacted" and "exposed," when applied to a cell, are used herein to describe the process by which a platinum(II) complex of this invention and a gene therapeutic construct, a chemotherapeutic, or radiotherapeutic agent are delivered to a target cell or are placed in direct juxtaposition with the target cell. To achieve cell killing or stasis, both agents are delivered to a cell in a combined amount effective to kill the cell or prevent it from dividing.

The therapeutic compositions of the present invention are advantageously administered in the form of injectable compositions either as liquid solutions or suspensions, solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. These preparations also may be emulsified. A typical composition for such purpose comprises a pharmaceutically acceptable carrier. For instance, the composition may contain 10 mg, 25 mg, 50 mg or up to about 100 mg of human serum albumin per milliliter of phosphate buffered saline. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers, and the like. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, saline solutions, parenteral vehicles such as sodium chloride, Ringer's dextrose, *etc.* Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial agents, anti-oxidants, chelating

agents, and inert gases. The pH and exact concentration of the various components in the pharmaceutical composition are adjusted according to well known parameters.

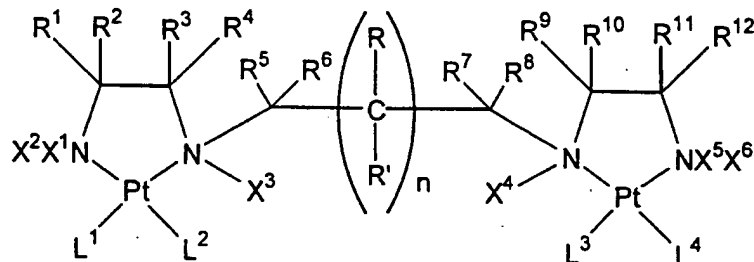
Additional formulations are suitable for oral administration. Oral formulations include such typical excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. The compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations, or powders. When the route is topical, the form can be a cream, ointment, salve, or spray.

Although the description above contains many specifics, these should not be construed as limiting the scope of the invention, but as merely providing illustrations of some of the presently preferred embodiments of this invention. For example, the compounds can be made in pure water instead of the mixture of methanol and water. Thus the scope of this invention should be determined by the appended claims and their legal equivalents, rather than by the examples given.

## CLAIMS

I Claim:

1. A complex of the formula (I):



where n is 0, 1, 2, 3, 4, 5, or 6;

each of L<sup>1</sup>, L<sup>2</sup>, L<sup>3</sup>, and L<sup>4</sup>, independently, is Cl or Br;

each of R, R', R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup>,

independently, is hydrogen, lower alkyl, lower alkoxy, alkyl carboxylate or alkyl carboxylic acid salt; or each of CR<sup>1</sup>R<sup>2</sup> (that is, R<sup>1</sup> and R<sup>2</sup> together with the carbon which they substitute), CR<sup>3</sup>R<sup>4</sup>, CR<sup>5</sup>R<sup>6</sup>, CR<sup>7</sup>R<sup>8</sup>, CR<sup>9</sup>R<sup>10</sup>, CR<sup>11</sup>R<sup>12</sup>, and CRR',

independently, is C=O; and

each of X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>, and X<sup>6</sup>, independently, is hydrogen, lower alkyl, alkyl carboxylate or alkyl carboxylic acid salt.

2. The complex of claim 1, which is a 2:1 complex of tetrachloroplatinum (II) and triethylenetetraamine.

3. The complex of claim 1, which is a 2:1 complex of tetrachloroplatinum (II) and N,N'-bis(2-dimethylaminoethyl)oxamide.

4. Use of a therapeutically effective amount of the complex of Claim 1 for the treatment of cancer.
5. Use of a therapeutically effective amount of the complex of Claim 1 for the treatment of AIDS (Acquired Immune Deficiency Syndrome).
6. A pharmaceutical composition comprising cisplatin and folic acid, wherein said pharmaceutical composition has a mole ratio of cisplatin to folic acid in the range of about 1:0.05 to 1:1.
7. The composition of Claim 6, wherein the ratio of cisplatin to folic acid is about 1:0.1 to 1:0.8.
8. The composition of Claim 6, wherein the ratio of cisplatin to folic acid is about 1:0.2 to 1:0.5.
9. The composition of claim 6, further comprising pharmaceutical excipients.
10. The composition of claim 4, wherein the pharmaceutical excipient is sodium bicarbonate, mannitol, lactose, sodium chloride, phosphates, water, ethanol, hydrochloric acid, magnesium stearate, cellulose, starch, polyethylene glycol, or a mixture thereof.
11. Use of a therapeutically effective amount of the composition of claim 6 for the treatment of cancer.
12. Use of a therapeutically effective amount of the composition of claim 6 for the treatment of AIDS (Acquired Immune Deficiency Syndrome).

13. Use according to claim 12, further comprising co-administering AZT (Azidothymidine).

14. A complex with the formula  $cis\text{-Pt(II)}L^1L^2$ , wherein each of  $L^1$  and  $L^2$ , independently, is the carboxylate of phosphatidylserine, the derivative of an  $\alpha$ -amino acid, or the derivative of a  $\beta$ -amino acid, wherein each ligand is bidentate with  $\text{-NH}_2$  and  $\text{-COO}^-$  as binding site.

15. Use of a complex of the formula  $cis\text{-Pt(II)}L^1L^2$ , wherein each of  $L^1$  and  $L^2$ , independently, is the carboxylate of phosphatidylserine, an  $\alpha$ -amino acid, a  $\beta$ -amino acid, the derivative of an  $\alpha$ -amino acid, or the derivative of a  $\beta$ -amino acid, wherein each ligand is bidentate with  $\text{-NH}_2$  and  $\text{-COO}^-$  as binding sites for the treatment of cancer.

16. Use according to claim 15 wherein said cancer is breast cancer, prostate cancer, lung cancer, colon cancer, or skin cancer.

17. A pharmaceutical composition comprising:

a) a pharmaceutically acceptable dosage form of a complex with the formula  $cis\text{-Pt(II)}L^1L^2$ , wherein each of  $L^1$  and  $L^2$ , independently, is the carboxylate of phosphatidylserine, an  $\alpha$ -amino acid, a  $\beta$ -amino acid, the derivative of an  $\alpha$ -amino acid, or the derivative of a  $\beta$ -amino acid, wherein each ligand is bidentate with  $\text{-NH}_2$  and  $\text{-COO}^-$  as binding sites; and

b) a pharmaceutically acceptable buffer, solvent, or diluent.

18. Use of a therapeutically effective amount of the pharmaceutical composition of claim 17 for the treatment of cancer.

19. Use according to claim 18 wherein said cancer is breast cancer, prostate cancer, lung cancer, colon cancer, or skin cancer.

20. Use according to claim 18 wherein said pharmaceutical composition comprises about 10 mg to about 1000 mg of said complex.

21. Use according to claim 18 wherein said pharmaceutical composition is administered once every one to four weeks.

22. Use according to claim 21 wherein the administration of said pharmaceutical composition is repeated until remission of said cancer is observed.

23. Use according to claim 18 wherein the administration of said pharmaceutical composition is oral.

24. Use according to claim 18 wherein the administration of said pharmaceutical composition is parenteral.

25. Use according to any of claims 4, 11, or 18 further comprising administration of an additional cancer therapeutic agent to a cancer patient.

26. Use according to claim 25 wherein said additional cancer therapeutic agent is selected from the group consisting of irradiation, a chemotherapeutic agent, and an expression construct comprising a nucleic acid encoding a cancer therapeutic gene and a promoter operative in eukaryotic cells, wherein said nucleic acid is operatively linked to said promoter.

27. Use according to claim 25, wherein said additional cancer therapeutic agent is a DNA damaging agent selected from the group consisting of verapamil, podophyllotoxin, procarbazine, mechlorethamine, cyclophosphamide, camptothecin, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin,



etoposide (VP16), tamoxifen, taxol, transplatin, 5-fluorouracil, vincristin, vinblastin, and methotrexate.

28. Use according to claim 26, wherein said irradiation is selected from the group consisting of X-ray radiation, UV-radiation,  $\gamma$ -radiation, and microwave radiation.

29. Use according to claim 26, wherein said nucleic acid is a cDNA or genomic DNA.

30. Use according to claim 26, wherein said expression construct is selected from the group consisting of an adenovirus, an adeno-associated virus, a vaccinia virus, and a herpes virus.

31. Use according to claim 26, wherein said nucleic acid encodes a therapeutic gene selected from the group consisting of p53, p16, p21, MMAC1, p73, zac1, C-CAM, BRCA1, Rb, Bax, Bak, Bim, Bik, Bid, Bad gene Harakiri, Ad E1B, an ICE-CED3 protease, and a cytokine.

32. Use according to any of claims 4, 11, or 18, wherein said administration is effected by local delivery of said pharmaceutical composition.

33. Use according to any of claims 4, 11, or 18, wherein said administration is effected by direct injection of a tumor in said cancer patient with said pharmaceutical composition.

34. Use according to any of claims 4, 11, or 18, wherein said administration comprises delivering said pharmaceutical composition endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously or intratumorally.

35. Use according to any of claims 4, 11, or 18, further comprising the step, prior to said administration, of resection of a tumor in said cancer patient.

36. A complex comprising ligands in free acid form with the formula  $cis\text{-Pt(II)Cl}_2\text{L}^3\text{L}^4$ ,  $cis\text{-Pt(II)Br}_2\text{L}^3\text{L}^4$  or  $cis\text{-Pt(II)(NO}_3)_2\text{L}^3\text{L}^4$ , wherein each of  $\text{L}^3$  and  $\text{L}^4$ , independently is phosphatidylserine, an  $\alpha$ -amino acid, a  $\beta$ -amino acid, a derivative of an  $\alpha$ -amino acid, or the derivative of a  $\beta$ -amino acid, wherein each ligand is monodentate with  $\text{-NH}_2$  as a binding site.

Dose-Dependent Effect on Hep 3B Cell Viability

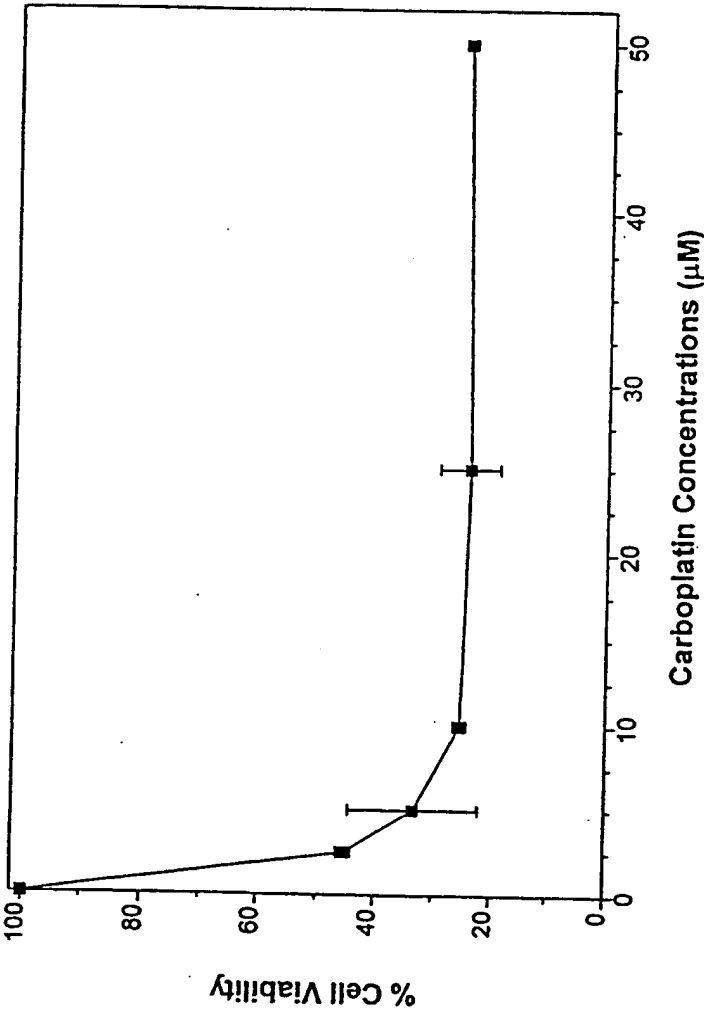


FIGURE 1

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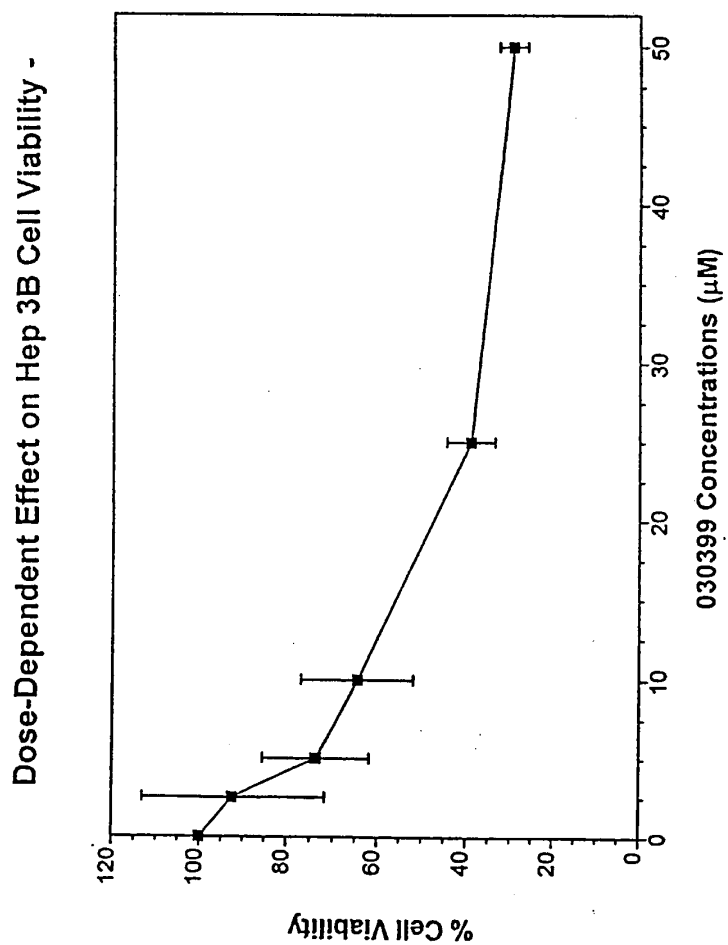


FIGURE 2

3/3

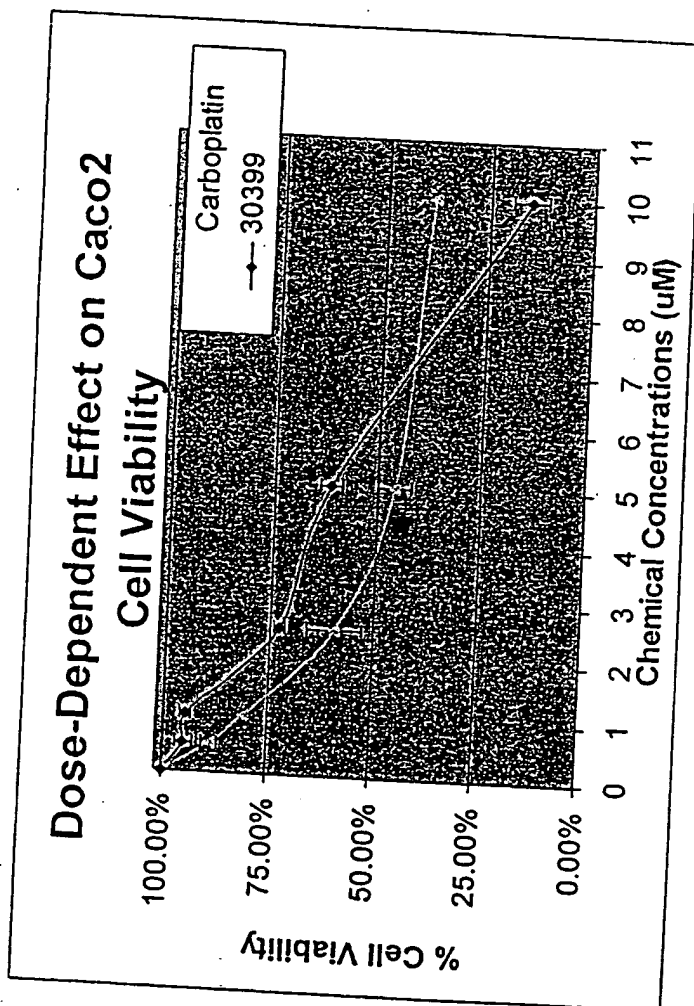


FIGURE 3

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/10881

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07F 15/00; A61K 31/28

US CL : 424/181.1, 208.1; 514/492; 536/23.1; 556/137

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/492; 556/137

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
REGISTRY and CA Databases

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category*           | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.             |
|---------------------|--|-----------------------------------|
| X,P<br>-----<br>Y,P | MILLER et al. Synthesis and biological activity of cis-dichloro mono- and bis(platinum) complexes with N-alkyl-ethylenediamine ligands. Inorganica Chimica Acta. 15 July 1999, Vol. 290, No. 2, pages 237-246, especially pages 244 and 245. | 1, 2, 4, and 10<br>-----<br>32-34 |
| X<br>-----<br>Y     | US 4,228,090 A (HYDES et al.) 14 October 1980, see column 2, lines 16-68.  | 14<br>-----<br>15-28, 32, and 34  |
| A,P                 | US 5,922,689 A (SHAW) 13 July 1999, see entire document.   | 6-15 and 25-35                    |
| A                   | US 5,844,001 A (MCCLAY et al.) 01 December 1998, see entire document.  | 6-35                              |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\*

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\*

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\*

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*A\*

document member of the same patent family

Date of the actual completion of the international search

13 JULY 2000

Date of mailing of the international search report

17 AUG 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/10881

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:  
1-35
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/10881

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-5, drawn to a dinuclear platinum complex of the formula (I) and uses.

Group II, claim(s) 6-13, drawn to a pharmaceutical composition and uses.

Group III, claim(s) 14-24, drawn to a mononuclear platinum chelate, pharmaceutical composition containing said chelate and uses.

Group IV, claim 36, drawn to a mononuclear platinum complex.

Linking claims 25-35, which read on Groups I-III will be examined to the extent that they read in said groups.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: they are directed to different inventions which contain different features in each of the groups. For example, Group I is a dinuclear platinum complex whereas Group IV is a mononuclear platinum complex. Group III is a metal chelate whereas Group II is not a metal chelate.



CORRECTED VERSION

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 October 2000 (26.10.2000)

PCT

(10) International Publication Number  
WO 00/63219 A1

(51) International Patent Classification<sup>7</sup>: C07F 15/00,  
A61K 31/28

(21) International Application Number: PCT/US00/10881

(22) International Filing Date: 20 April 2000 (20.04.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/130,530 21 April 1999 (21.04.1999) US  
09/552,167 18 April 2000 (18.04.2000) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,  
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,  
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,  
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ,  
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,  
TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent  
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent  
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,  
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

(48) Date of publication of this corrected version:

14 June 2001

(15) Information about Correction:

see PCT Gazette No. 24/2001 of 14 June 2001, Section II

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: PLATINUM COMPLEXES FOR THE TREATMENT OF CANCER

(57) Abstract: The synthesis and use of a series of novel platinum complexes for the treatment of cancer and AIDS are disclosed. The platinum complexes include cisplatin analogs, carboplatin analogs, and cisplatin and folic acid compounds.

WO 00/63219 A1

